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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

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INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
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Additional inventors are being named on the _____ separately numbered sheets attached hereto

TITLE OF THE INVENTION (500 characters max)

ANTI-CANCER THERAPIES

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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OR

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ENCLOSED APPLICATION PARTS (*check all that apply*)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

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Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 333854549 US, in an envelope addressed to: MS Provisional Patent Application, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

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PROVISIONAL PATENT APPLICATION

ANTI-CANCER THERAPIES

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DESCRIPTION

For treatment of cancer, glufosfamide and gemcitabine can be administered in combination to a subject in need of treatment for cancer. A variety of cancers can be treated by this method. An example of a cancer that can be treated by this method is pancreatic cancer. A third agent with antitumor activity, such as bevacizumab, irinotecan, exatecan, pemetrexed, or cisplatin, can be administered in combination with glufosfamide and gemcitabine.

For treatment of cancer, glufosfamide and bevacizumab can be administered in combination to a subject in need of treatment for a cancer. A variety of cancers can be treated by this method. An example of a cancer that can be treated by this method is colorectal cancer.

For treatment of cancer, glufosfamide and an anticancer agent selected from the group consisting of irinotecan, exatecan, pemetrexed, and cisplatin can be administered in combination to a subject in need of treatment for a cancer.

For treatment of breast cancer, glufosfamide can be administered to a subject in need of treatment for breast cancer. For treatment of colorectal cancer, glufosfamide can be administered to a subject in need of treatment for colorectal cancer. For treatment of gemcitabine-refractory pancreatic cancer, glufosfamide can be administered to a subject in need of treatment for gemcitabine-refractory pancreatic cancer. For the aforementioned treatment of

breast cancer, colorectal cancer, and gemcitabine-refractory pancreatic cancer, in some cases glufosfamide is administered as a single agent.

Glufosfamide, gemcitabine, bevacizumab, irinotecan, exatecan, pemetrexed, and cisplatin, as used in the present invention can be administered at any dose that is therapeutically effective, such as doses comparable to those routinely utilized clinically. Specific dose regimens for known and approved antineoplastic agents (e.g., the recommended effective dose) are known to physicians and are given, for example, in the product descriptions found in the PHYSICIANS' DESK REFERENCE, 2003, 57th Ed., Medical Economics Company, Inc., Oradell, N.J; Goodman & Gilman's THE PHARMACOLOGICAL BASIS OF THERAPEUTICS" 2001, 10^{th} Edition, McGraw-Hill, New York; and/or are available from the Federal Drug Administration and/or are discussed in the medical literature.

In a preferred embodiment, glufosfamide is administered for 1, 2, 3, 4, 5, 6, 7, 8, or more than 8 cycles, each cycle comprising:

a) infusion of about 4500-5000 mg/m^2 glufosfamide over an infusion period of 1-6 hours once every three weeks;

b) infusion of about 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours three consecutive days (days 1, 2 and 3) every three weeks; or

c) infusion of about 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours once per week.

As used in this context an "infusion period of 1-6 hours" includes an infusion period of about 1, about 2, about 3, about 4, about 5 and about 6 hours.

In a preferred embodiment, gemcitabine is administered on weeks 1, 2, 3, 5, 6 and 7 of a seven-week cycle, and the administration is for 1, 2, 3, 4, or more than 4 seven–week cycles, where each cycle comprises:

a) infusion of about 1000 mg/m^2 gemcitabine over a period of about 30 min;

b) infusion of about 2200 mg/m^2 gemcitabine over a period of about 30 min;

c) infusion of about 1500 mg/m^2 gemcitabine over a period of about 150 min.

Administration Regimens

It will be appreciated that chemotherapy for cancer sometimes involves multiple "rounds" or "cycles" of administration of a drug, where each cycle comprises administration of the drug one or more times according to a specified schedule (e.g., every three weeks for three consecutive days; once per week; *etc.*). For example, chemotherapeutic drugs can be administered for from 1 to 8 cycles, or for a longer period. When more than one drug (e.g., two drugs) is administered to a subject, each can be administered according to its own schedule (e.g., weekly; once every three weeks; *etc.*). It will be clear that administration of drugs, even those administered with different periodicity, can be coordinated so that both drugs are administered on the same day at least some of the time or, alternatively, so the drugs are administered on consecutive days at least some of the time.

In treatment regimens in which glufosfamide and gemcitabine are administered in combination, they can be administered in any order. In certain embodiments, glufosfamide is administered one day before, one day after, or the same day as, administration of gemcitabine. It will be understood that other schedules can be used as determined by the physician.

As is understood in the art, treatment with cancer therapeutic drugs can be suspended temporarily if toxicity is observed, or for the convenience of the patient, without departing from the scope of the invention, and then resumed.

Administration In Combination

Two or three drugs are administered to a subject "in combination" when the drugs are administered as part of the same course of therapy. A course of therapy refers to administration of combinations of drugs believed by the medical professional to work together additively, complementarily, synergistically, or otherwise to produce a more favorable outcome than that anticipated for administration of a single drug. A course of therapy can be for one or a few days, but more often extends for several weeks.

Thus, an example of administration in combination is administration of glufosfamide once every three weeks for 1 to 8 three-week cycles beginning on day 1, and administration of gemcitabine once each week for weeks 1, 2, 3, 5, 6, and 7 of a seven-week cycle for one or more seven-week cycles. In an embodiment administration of gemcitabine begins on day 1, day -1, or day 2 or another day that with the cycle.

When two drugs are administered in combination, a variety of schedules can be used. In one case, for example and without limitation, Drug 1 is first administered prior to administration of Drug 2, and treatment with Drug 1 is continued throughout the course of administration of Drug 2; alternatively Drug 1 is administered after the initiation or completion of Drug 2 therapy; alternatively, Drug 1 is first administered contemporaneously with the initiation of the other cancer therapy. As used in this context, "contemporaneously" means the two drugs are administered the same day, or on consecutive days.

Although in principle certain drugs can be co-formulated, in general they are administered in separate compositions Similarly, although certain drugs can be administered simultaneously, more often (especially for drugs administered by infusion) drugs are administered at different times on the same day, on consecutive days, or according to another schedule.

In some cases a chemotherapeutic drug, e.g., glufosfamide, is administered as a "single agent," i.e., not administered "in combination" with another antitumor drug.

Cancers

The methods of the present invention can be used for treatment of any cancer, including but not limited to breast cancer, pancreatic cancer, cancer of the colon and/or rectum, leukemia, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, brain cancer, cancer of the larynx, gallbladder, parathyroid, thyroid, adrenal, neural tissue, head and neck, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell carcinoma, primary brain tumor, acute and chronic lymphocytic and granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, ovarian

tumor, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumor, polycythermia vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

Certain treatment regimens of the invention are particularly suited for treatment of pancreatic cancer, breast cancer, or colorectal cancer, as noted above. Thus, in certain embodiments of the invention the subject to whom treatment is administered has colorectal cancer or metastatic colorectal cancer. Colorectal cancer or metastatic colorectal cancer is currently treated by radiation therapy, surgery, and/or chemotherapy (e.g., administration of fluorouracil). In certain embodiments of the invention the subject to whom treatment is administered has breast cancer. Breast cancer is commonly treated by various combinations of surgery, radiation therapy, chemotherapy, and hormone therapy. In certain embodiments of the invention the subject to whom treatment is administered has pancreatic cancer. Among pancreatic cancers, chemotherapy-refractory pancreatic cancers, such as pancreatic cancers refractory to treatment with gemcitabine (see, e.g., Araneo et al., 2003, *Cancer Invest.* 21:489-96; Kozuch et al., 2001, *The Oncologist* 6:488-95; Noble and Goa, 1997, *Drugs* 54: 447-72N; Stephens et al., 1998, *Oncol. Nurs. Forum* 25:87-93; Burris and Storniolo, 1997, *Eur. J. Cancer* 33: Suppl 1:S18-22; Rothenberg et al., 1996, *Ann. Oncol.* 7:347-53) can be treated using the methods disclosed herein, e.g., by administration of glufosfamide. Serum carbohydrate 19-9 reportedly can be a useful marker for evaluating the response to gemcitabine therapy in pancreatic cancer (Ziske et al., 2003, *Br. J. Cancer* 89:1413-17).

Subject

A subject is a mammal in need of treatment for cancer. Generally, the subject is a human patient. In some embodiments of the invention, the subject can be a non-human mammal such as a non-human primate, an animal model (e.g., animals such as mice and rats used in screening, characterization and evaluation of medicaments) and other mammals.

Treatment

As used herein, and as well-understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, alleviation or amelioration of one or more symptoms, diminishment of extent of disease, stabilized (i.e., not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

Chemotherapeutic Agents

The following section describes drugs used in various embodiments of the invention. As these drugs are well known, only brief discussions are provided. Publications cited in this section are intended to illustrate aspects of the drug for the benefit of the practitioner; however, citation to a particular publication in this section or elsewhere in this disclosure is not intended to limit the present invention in any respect, including as to doses, combinations, and indications.

Glufosfamide

The antitumor drug glufosfamide (β-D-glucosyl-ifosfamide mustard; glc-IPM) is an alkylating agent used for treatment of cancer (see U.S. Patent No. 5,622,936 and Niculescu-Duvaz, 2002, *Curr Opin Investig Drugs* 3:1527-32). The alkylating moiety is glycosidically linked to ß-D-glucose, and cellular uptake of glufosfamide may be mediated by a sodium-dependent trans-membrane transporter protein of glucose (Briasoulis *et al.*, 2000, *J Clin Oncol* 18:3535-44). In phase II clinical studies, glufosfamide has been administered to patients with pancreatic cancer receiving first line treatment and in patients with non-small cell lung cancer receiving second line chemotherapy, as well as glioblastoma, breast cancer and colon cancer patients (see Niculescu-Duvaz, 2002, *supra*). Glufosfamide is routinely administered intravenously; it is contemplated that in the practice of the present invention other administration routes also can be used, such as intrathecal administration, intratumoral injection, oral administration and others. Glufosfamide can be administered at doses comparable to those

routinely utilized clinically (see Niculescu-Duvaz, 2002, *supra*). In preferred embodiments, glufosfamide is administered as described elsewhere herein.

Gemcitabine

Gemcitabine (2'-deoxy-2',2'-difluoro-cytidine, also known as 1-(4-amino-2-oxo-1H-pyrimidin-1-yl)-2-desoxy-2,2-difluororibose) is a nucleoside analogue that disrupts the process of cell replication. See U.S. Pat. Nos. 4,808,614 and 5,464,826. Gemcitabine HCl (Gemzar™; Lilly) has been used for treatment of patients with non-small cell lung cancer and pancreas cancer. See www. gemzar.com. Gemcitabine HCl is routinely formulated as a sterile solution and is administered by intravenous infusion. Other salt forms, e.g., the monophosphate, sulfate, malonate, citrate, and succinate are readily prepared, and can be utilized if desired. It is contemplated that other administration routes can be used, including intratumor injection, intrathecal administration, and others. In preferred embodiments, gemcitabine is administered as described elsewhere herein.

Bevacizumab

Bevacizumab (Avastin™; Genentech) is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody that has been developed as an anti-angiogenesis agent for treatment of cancers such as colorectal cancer, non-small-cell lung cancer, breast cancers, and other solid tumors. *See* Salgaller, 2003, *Curr Opin Mol Ther*, 5:657-67 and PCT applications WO 96/30046, and WO 98/45331. Bevacizumab as used in the present invention can be administered at doses comparable to those routinely utilized clinically (see, e.g., Yang 2003, *N Eng J. Med*, 349:419-21 and Cobleigh et al., 2003, *Semin Oncol.* 30(5 Suppl 16):117-24.

Irinotecan

Irinotecan (CPT-11, Camptosar®; Pharmacia & Upjohn) is a semisynthetic derivative of the plant alkaloid camptothecin that inhibits topoisomerase I. It has been developed as an anti-cancer drug for the treatment of colorectal cancer. Irinotecan can be administered at doses comparable to those routinely utilized clinically. For example, and without limitation, patients can receive Camptosar® in a 90-minute infusion once every 3 weeks. The starting dose for most patients can be 350 mg/m^2, but the dose may decrease to 300 mg/m^2 for patients 70 years of age

or older. Camptosar® can also be administered according to a weekly dosing schedule starting at 125 mg/m^2. The dose can be give for about 2 to 4 weeks, with course repeated every 7 weeks. See http://www.meds.com/colon/camptosar/treatment.html. Also see Rothenberg et al., 1996, *J Clin Oncol.* 14:1128-35.

Exatecan

Exatecan mesylate (DX-8951f; Daiichi Pharmaceutical Co.) is a water soluble analogue of the plant alkaloid camptothecin that inhibits topoisomerase I. Exatecan mesylate has been developed as a therapeutic agent for the treatment of non-small cell lung cancer, ovarian, tubal or peritoneal cancer, and breast cancer. Various dosages and administrations of exatecan mesylate for the treatment of cancers have been described. See, e.g., Verschraegen et al, 2004, *Cancer Chemother Pharmacol.* 53:1-7; Esteva et al, 2003, *Cancer* 98:900-7; Braybrooke et al., 2003, *Lung Cancer*, 41:215-9; Royce et al., 2004, *Invest New Drugs.* 22:53-61.

Pemetrexed

Pemetrexed (Alimta™), is an antifolate that inhibits thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase. Pemetrexed is active against pancreatic cancer cell lines *in vitro* and has shown activity in patients with advanced pancreatic cancer. See Kindler, 2002, *Semin Oncol.* 29:49-53 and Adjei, 2003, *Expert Rev Anticancer Ther.* 3:145-56.

Cisplatin

Cisplatin (cis-diaminedichloroplatinum (II)) is a divalent inorganic water soluble platinum containing complex with a broad activity as an antineoplastic agent (see Go and Adjei, 1999, *J Clin Oncol.* 17:409-22).

Equivalents and Incorporation by Reference

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes can be made and equivalents can be substituted without departing from the scope of the invention. In addition, many modifications can be made to adapt a particular situation, material, composition

of matter, process, process step or steps, to achieve the benefits provided by the present invention without departing from the scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an indication that any such document is pertinent prior art, nor does it constitute any admission as to the contents or date of the same.

Claims

1. A method of treatment comprising administering glufosfamide and gemcitabine in combination to a subject in need of treatment for cancer.

2. The method of claim 1 wherein the cancer is pancreatic cancer.

3. The method of claims 1-2 wherein glufosfamide is administered for 1, 2, 3, 4, 5, 6, 7, 8 or more than 8 dosage cycles, each cycle comprising:

a) infusion of 4500-5000 mg/m^2 glufosfamide over an infusion period of 1-6 hours once every three weeks;

b) infusion of 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours three consecutive days every three weeks; or

c) infusion of 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours once per week.

4. The method of any of claims 1-3 wherein gemcitabine is administered on weeks 1, 2, 3, 5, 6 and 7 of a seven-week dosage cycle, wherein said administration is for 1, 2, 3, 4 or more than 4 seven–week cycles, and wherein each cycle comprises:

a) infusion of 1000 mg/m^2 gemcitabine over a period of about 30 min;

b) infusion of 2200 mg/m^2 gemcitabine over a period of about 30 min;

c) infusion of 1500 mg/m^2 gemcitabine over a period of about 150 min.

5. The method of claim 4 wherein the administration of gemcitabine is one day before, one day after, or the same day as, the administration of glufosfamide.

6. A method of treatment comprising administering glufosfamide to a subject in need of treatment for a gemcitabine-refractory pancreatic cancer.

7. The method of claim 6 wherein glufosfamide is administered for 1, 2, 3, 4, 5, 6, 7, 8 or more than 8 dosage cycles, each cycle comprising:

a) infusion of 4500-5000 mg/m^2 glufosfamide over an infusion period of 1-6 hours once every three weeks;

b) infusion of 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours three consecutive days every three weeks; or

c) infusion of 1500 mg/m^2 glufosfamide over an infusion period of 1-6 hours once per week.

Application Data Sheet

Application Information

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Sequence submission?::	None
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